7 Department for Environment, Food and Rural Affairs. BSE Statistics. 2005, Published online at http://www.defra.gov.uk/animalh/bse/statistics/incidence.html. Accessed September 2005.

8 Priola S, Vorberg I. Molecular aspects of disease pathogenesis in the transmissible spongiform encephalopathies. *Methods Mol Biol* 2004; 268: 517–40.

9 Prusiner SB. Biology and genetics of prion diseases. *Ann Rev Microbiol* 1994; 48: 655–86.

10 Roma AA, Prayson RA. Bovine spongiform encephalopathy and variant Creutzfeldt–Jakob disease: how safe is eating beef? *Cleve Clin J Med* 2005; 72: 185–6, 189–90, 192–4.

11 Centers for Disease Control and Prevention. BSE (bovine spongiform encephalopathy, or mad cow disease), second BSE-positive cow identified in the United States. Revised June 27, 2005. Published online at http://www.cdc.gov/ncidod/dvrd/bse/bse_cow_june_2005.htm. Accessed September 2005.

12 Ironside JW, Ritchie DL, Head MW. Phenotypic variability in human prion diseases. *Neuropathol Appl Neurobiol* 2005; 31: 565–79.

13 Ward HJT, Everington D, Croes EA *et al.* Sporadic Creutzfeldt–Jakob disease and surgery: a case-control study using community controls. *Neurology* 2002; 59: 543–8.

14 Trevitt CR, Singh PN. Variant Creutzfeldt–Jakob disease: pathology, epidemiology, and public health implications. *Am J Clin Nutr* 2003; 78: 651–66.

15 Goldfarb LG, Brown P, Cervenakova L, Gajdusek DC. Molecular genetic studies of Creutzfeldt–Jakob disease. *Mol Neurobiol* 1994; 8: 89–97.

16 Kovács GS, Trabattoni G, Hainfellner JA, Ironside JW, Knight RSG, Budka H. Mutations of the prion protein gene: phenotypic spectrum. *J Neurol* 2002; 249: 1567–82.

17 Brown P, Preece M, Brandel J-P *et al.* Iatrogenic Creutzfeldt–Jakob disease at the millennium. *Neurology* 2000; 55: 1075–81.

18 Bruce ME, Will RG, Ironside JW *et al.* Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. *Nature* 1997; 389: 498–501.

19 Scott MR, Will R, Ironside J *et al.* Compelling transgenetic evidence for transmission of bovine spongiform encephalopathy prions to humans. *Proc Natl Acad Sci USA* 1999; 96: 15137–42.

20 Houston F, Foster JD, Chong A, Hunter N, Bostock CJ. Transmission of BSE by blood transfusion in sheep. *Lancet* 2000; 356: 999–1000.

21 Cervenakova L, Yakoleva O, McKenzie C *et al.* Similar levels of infectivity in the blood of mice infected with human-derived vCJD and GSS strains of transmissible spongiform encephalopathy. *Transfusion* 2003; 43: 1687–94.

22 Lee CA, Ironside JW, Bell JE *et al.* Retrospective neuropathological review of prion disease in UK haemophilic patients. *Thromb Haemost* 1998; 80: 909–11.

23 Evatt BL. Prions and haemophilia: assessment of risk. *Haemophilia* 1998; 4: 628–33.

24 Esmonde TF, Will RG, Slattery JM *et al.* Creutzfeldt–Jakob disease and blood transfusion. *Lancet* 1993; 341: 205–7.

25 Ironside JW, Head MW, Bell JE, McCardle L, Will RG. Laboratory diagnosis of variant Creutzfeldt–Jakob disease. *Histopathology* 2000; 37: 1–9.

26 Clark P, Ghani A. Projections of the future course of the primary vCJD epidemic in the UK: inclusion of subclinical infection and the possibility of wider genetic susceptibility. *J R Soc Interface* 2005; 2: 19–31.

27 Owen F, Poulter M, Collinge J, Crow TJ. Codon 129 changes in the prion protein gene in Caucasians. *Am J Hum Genet* 1990; 46: 1215–6.

28 Collinge J, Palmer MS, Dryden AJ. Genetic predisposition to iatrogenic Creutzfeldt–Jakob disease. *Lancet* 1991; 337: 1441–2.

29 Alperovitch A, Zerr I, Pocchiari E *et al.* Codon 129 prion protein genotype and sporadic Creutzfeldt–Jakob disease. *Lancet* 1999; 353: 1673–4.

30 MacGregor I. Prion protein and developments in its detection. *Transfus Med* 2001; 11: 3–14.

31 Ironside JW, McCardle L, Horsburgh A, Lim Z, Head MW. Pathological diagnosis of variant Creutzfeldt–Jakob disease. *APMIS* 2002; 110: 79–87.

32 Wadsworth JD, Joiner S, Hill AF *et al.* Tissue distribution of protease resistant prion protein in variant Creutzfeldt–Jakob disease using a highly sensitive immunoblotting assay. *Lancet* 2001; 358: 171–80.

33 Safar JG, Geschwind MD, Deering C *et al.* Diagnosis of human prion disease. *Proc Natl Acad Sci USA* 2005; 102: 3501–6.

34 Saborio GP, Permanne B, Soto C. Sensitive detection of pathological prion protein by cyclical amplification of protein misfolding. *Nature* 2001; 411: 810–3.

35 Castilla J, Saa P, Soto C. Detection of prions in blood. *Nat Med* 2005; 11: 982–5.

36 CJD Incidents Panel. *Management of Possible Exposure to CJD through Medical Procedures: Framework Document.* UK, 2005. Published online at http://www.hpa.org.uk/infections/topics_az/cjd/framework_Aug%202005.pdf. Accessed September 2005.

37 Ironside JW, Hilton DA, Ghani A *et al.* Retrospective study of prion-protein accumulation in tonsil and appendix tissues. *Lancet* 2000; 355: 1693–4.

38 Hilton DA, Ghani AC, Conyers L *et al.* Prevalence of lymphoreticular prion protein accumulation in UK tissue samples. *J Pathol* 2004; 203: 733–9.

39 Llewelyn CA, Hewitt PE, Knight RSG *et al.* Possible transmission of variant Creutzfeldt–Jakob disease by blood transfusion. *Lancet* 2004; 363: 417–21.

40 Peden AH, Head MW, Ritchie DL, Bell JE, Ironside JW. Preclinical vCJD after blood transfusion in a PRNP codon 129 heterozygous patient. *Lancet* 2004; 364: 527–9.

41 Det Norske Veritas for Department of Health. *Risk Assessment of vCJD Infectivity in Blood.* Appendix II.

Infectivity of Blood. February 2003. Published online at http://www.dnv.com/binaries/AppII_tcm4-74416.pdf. Accessed September 2005.

42 Health Protection Agency. *Variant Creutzfeldt–Jakob Disease (vCJD) and Plasma Products*. Clinical information. 2004. Published online at http://hpa.org.uk/infections/topics_az/cjd/Clinical.pdf. Accessed September 2005.

43 MacKenzie D. First human case of mad cow disease in Japan. NewScientist.com news service 2005. Published online at http://www.newscientist.com/channel/health/dn6971. Accessed September 2005.

44 Mitchell S. Japan vCJD case poses blood-donor concern. United Press International, June 23, 2005. Published online at http://www.newsdaily.com/index.php?feed=Science&article=UPI-1-20050623-18225000-bc-us-blood.xml. Accessed September 2005.

45 The National Creutzfeldt-Jakob Disease Surveillance Unit UK. Updated November 7, 2005. Published online at http://www.cjd.ed.ac.uk. Accessed November 2005.

別紙様式第2-1
番号1

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

| 識別番号・報告回数 | | | 報告日 | 第一報入手日<br>2006年4月21日 | 新医薬品等の区分<br>該当なし | 厚生労働省処理欄 |
|---|---|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 一般的名称 | ①②人血清アルブミン<br>③④乾燥濃縮人アンチトロンビンⅢ<br>⑤人ハプトグロビン<br>⑥乾燥濃縮人血液凝固第Ⅷ因子 | 研究報告の公表状況 | J Neurol. Neurosurg. Psychiatry online/ doi:10:1136/jnnp:073395 | 公表国<br>イギリス |
| 販売名（企業名） | ①献血アルブミン-Wf<br>②献血アルブミン(5%)-Wf<br>③ノイアート<br>④ノイアート静注用1500単位<br>⑤ハプトグロビン注-ヨシトミ<br>⑥コンコエイト-HT | | | |

**研究報告の概要**

CJDは、孤発型、遺伝型、医原型及び変異型の4つの臨床形態をとる。世界中で最もありふれた形態である孤発型CJDの原因は不明であり、2つの研究が以前に処置された外科的治療によるものと示唆しているものの、症例対照研究は何ら一貫性のある危険要因を確認することができていない。遺伝型CJDは、プリオン蛋白に内在する変異と関係し、これが一般的に直接的な原因と考えられている。しかし変異は多分、現在はまだ認められていないものの、感染源に対しての責任を増している。残り2つのCJDの型は、後天的なものである。変異型CJDは、BSEが原因と考えられ、これは汚染食品によるとされている。医原型CJDは、医療又は外科治療の行為によってCJDの不注意な感染に由来する。医原型CJDの内、2つの最も重要な事例は、死体からのヒトの成長ホルモン治療及び外科手術の際の硬膜移植片の使用によるものである。角膜移植、深部電極及び脳神経外科もまた、まれに関与していた。
硬膜関連CJDの最初の報告は1987年であり、より詳細な報告が翌年に公表された。硬膜関連CJDは現在までに、世界中で164の症例があることが認められている。本報告では、英国におけるサーベイランスで確認された硬膜移植関連CJDの7症例、及び最初のブタ硬膜レシピエントのCJD症例について報告及び記述する。
レシピエントは1988年に右の前頭部髄膜腫の切除術を受けた、そして、豚皮質移植片が硬膜を修復するのに用いられた。レシピエントは、134ヵ月後に頭痛、失調と認識減退を呈した。調査により明らかにされた特徴は、一貫して孤発型CJDであり、典型的な脳波によっても確認され、病理学的診断が下された。検死の結果、前頭および側頭の皮質に海綿状変化を示し、同様の特徴は大脳基底核、視床及び小脳にも認められた。免疫細胞化学検査はPrPの広範囲にわたる蓄積を示し、そして、ウエスタンブロット試験は1型アイソフォームを示した。
我々は、症例VIII（硬膜補修にブタの真皮を使用）がヒト以外の移植片に曝露されたヒトでの最初のCJD感染症例であると考える。発症年齢、潜伏期間、臨床並びに調査の特徴は孤発型CJDの典型例に似ていた。さらに、病理学的特徴もまた、孤発型CJDに特有なものと考えられ、1型$PrP^{Pres}$と確認された。いずれも、未確認の病原体感染の可能性を完全には排除することができない。しかし、ブタにおけるTSEは、動物モデルでの感染実験による感染でも現在認められていないことから、偶然によるとするのが、最も妥当な説明である。

**使用上の注意記載状況・その他参考事項等**

代表としてノイアート（献血）の記載を示す。
2. 重要な基本的注意
(1)略
1)略
2)現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的なvCJD等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

| 報告企業の意見 | 今後の対応 |
|---|---|
| 英国におけるサーベイランスにおいてブタの真皮を硬膜補修に用いた患者がCJDを発症したとするヒト以外の移植片に暴露されたヒトでの最初のCJD感染症例である。<br>ブタのTSEは動物実験においても認められていない。また、これまで血漿分画製剤によってスクレイピーを含むプリオン病が伝播したとの報告はない。しかしながら、万一TSE感染動物由来原材料が本剤の原料に混入した場合には、製造工程においてプリオンを低減し得るとの報告があるものの、製剤から伝播する可能性を完全には否定し得ない。そのため、弊社の血漿分画製剤の製造工程におけるTSE感染性低減に関する検証実験を加速し、自社データを早期に取得し、工程評価を行い、必要に応じて工程改善を実施する予定である。 | 本報告は本剤の安全性に影響を与えないと考えるので、特段の措置はとらない。 |



ヘパリン

JNNP Online First, published on April 20, 2006 as 10.1136/jnnp.2005.073395

BENE2006-019

SHORT REPORT

# Dura mater-associated Creutzfeldt–Jakob disease: experience from surveillance in the UK

C A Heath, R A Barker, T F G Esmonde, P Harvey, R Roberts, P Trend, M W Head, C Smith, J E Bell, J W Ironside, R G Will, R S G Knight

*J Neurol Neurosurg Psychiatry* 2006;000:1–3. doi: 10.1136/jnnp.2005.073395

Between 1970 and 2003, seven cases of human dura mater-associated Creutzfeldt–Jakob disease (CJD) were identified in the UK. Furthermore, we identified a case of CJD in a porcine dura graft recipient. The mean incubation period of the human dura mater cases was 93 (range 45–177) months. The clinico-pathological features of the cases are described and compared with cases previously reported in the world literature.

Creutzfeldt–Jakob disease (CJD) exists in four clinical forms: sporadic, genetic, iatrogenic and variant. The cause of sporadic CJD, the most common form worldwide, is unknown and case–control studies have failed to identify any consistent risk factor, although two studies have implicated previous surgical interventions.[1 2] Genetic forms of the disease are associated with underlying mutations of the prion protein gene (*PRNP*), which are generally considered to be directly causative.Mutations, however, possibly increase liability to some, as of yet unrecognised, source of infection. The two remaining forms of CJD are acquired. Variant CJD is considered to be caused by bovine spongiform encephalopathy,[3–5] through contaminated food products; iatrogenic CJD results from the inadvertent transmission of CJD during the course of medical or surgical treatment. The two most numerically significant instances of iatrogenic CJD resulted from treatment with cadaveric human growth hormone and the use of dura mater grafts in surgery. Corneal grafts, depth electrodes and neurosurgical instruments have also rarely been implicated.[6 7]

The first report of dura mater-associated CJD was published in 1987,[8] with a more detailed report appearing the following year;[9] to date, 164 cases have been recognised worldwide (P Brown, personal communication). This paper reports and describes the seven cases of human dura mater graft-associated CJD identified during surveillance in the UK and also, for the first time, reports a case of CJD in a porcine dura graft recipient.

## METHODS

CJD surveillance in the UK has been undertaken in four phases.

- A retrospective review was carried out in England and Wales from 1970 to 1979.
- A prospective study was carried out in England and Wales from 1980 to 1984.
- A retrospective review was conducted in UK to cover the period from 1985 to 1990.
- A prospective surveillance was instituted in the UK in 1990 and continues.

The methodology of the National CJD Surveillance Unit has been described in previous publications.[10 11]

## RESULTS

### Human dura mater

During the period between 1970 and 2003, seven cases of human dura mater-associated CJD were identified in the UK. Table 1 shows the basic demographic features. The latent period between surgery and the onset of CJD ranged from 45 to 177 (mean: 93) months. The mean age at surgery was 33 years, with a mean age at onset of 41 years.

Lyodura (B Braun Melsungen, Germany), a particular brand of human dura mater, was implicated in six of the seven cases (the manufacturer of the dura graft implicated in case I is unknown).

The six cases associated with Lyodura were exposed to the presumed source of "infection" between 1983 and 1987, with the first recognised case in the UK exposed to human dura mater in 1969.

A detailed account of both clinical and investigative features is available online. In four cases, the clinical phenotype at onset appears to correlate with the site of graft placement or underlying parenchymal damage (cases II, III, V and VI). For example—in case II, the initial illness presentation included a right visual field defect; a left hemisphere tumour was also diagnosed. The subsequent CJD began with a right visual field disturbance and progressed with signs indicating the involvement of the left hemisphere. Some of the cases were investigated before the widespread availability of MRI, and therefore MRI was only available in only four of the seven cases. None of the cases showed the characteristic radiological features of human prion disease[14] with post-surgical change being the most commonly recognised abnormality. Despite all seven cases having at least one electroencephalogram during the course of investigation, only three of the seven cases showed the "typical" features.

Autopsy was carried out in five of our seven cases. In general, the neuropathology was characterised by widespread spongiform change accompanied by variable neuronal loss and gliosis. Western blot analysis for $PrP^{res}$ was carried out in three cases (cases II, VI and VII). The mobility and glycoform ratio of the $PrP^{res}$ is indistinguishable from those of the type 1 $PrP^{res}$, identified in cases of sporadic CJD, and is distinct from type 2B, $PrP^{res}$ identified in variant CJD.

### Porcine dura mater

We believe the identification of CJD in a porcine graft recipient to be the first such report worldwide (table 1,case VIII). The recipient underwent excision of a right fronto-

Abbreviations: CJD, Creytzfeldt–Jakob disease

Case V received two dura grafts, is assumed that the first graft was responsible for transmission.

**Table 1** UK case details—human dura mater

| Case | Surgical procedure | Dura | Year of surgery | Year of death | Incubation period (Months) | Duration of illness (Months) |
|---|---|---|---|---|---|---|
| I, Esmonde *et al*[12] | Suboccipital craniotomy and C1/2 laminectomy for cerebellar ectopia and syringomyelia | ? | 1969 | 1979 | 104* | 6 |
| II, Esmonde *et al*[12] | Excision of a left temporal cortex meningioma | L | 1983 | 1991 | 93* | 5* |
| III | Repair surgical leak after acoustic neuroma excision | L | 1985 | 1989 | 51 | 2 |
| IV, Willison *et al*[13] | Posterior fossa decompression and cervical laminectomy for cerebellar ectopia or syringomyelia | L | 1985 | 1989 | 45* | 4 |
| V | Excision of a left parietal cortex meningioma | 1) L | 1985 | 1993 | 1) 86 | 11 |
| | | 2) L | 1986 | | 2) 79 | |
| VI | Excision of a cerebellar astrocytoma | L | 1986 | 1997 | 103 | 33 |
| VII | Excision of a eosinophilic granuloma right frontal region skull | L | 1987 | 2003 | 177 | 5 |
| Porcine Dura Graft: | | | | | | |
| VIII | Excision of a right frontoparietal meningioma | P | 1988 | 2000 | 134 | 3 |

*Revised from previously published figures.
L, Lyodura; P, Porcine dura.

parietal meningioma in 1988 and a zenoderm graft was used to repair the dura. The recipient presented with headaches, ataxia and cognitive decline after 134 months. Investigative features were consistent sporadic CJD, with a typical electroencephalogram was identified, and pathological confirmation was obtained. Autopsy showed spongiform change in the frontal and temporal cortex, with similar features identified in the basal ganglia, thalamus and cerebellum. Immunocytochemistry for PrP showed widespread accumulation and western blot analysis showed the type 1 isoform.

## DISCUSSION

Human dura mater is a rare, but important source of transmission of human prion disease, with only seven cases recognised in a 33-year period. Surveillance systems worldwide have identified 164 cases of CJD in people previously exposed to human dura mater. Prevalence is particularly high in Japan and probably reflects neurosurgical practice, with an estimated 20 000 grafts used each year.[15] The overall risk of CJD associated with human dura grafts in the UK is unknown because an accurate estimation of human dura graft use and thus a denominator for calculation of risk is not available. The estimated risk after exposure in Japan has been estimated to be approximately 1 per 2000 patients treated between 1979 and 2000 and approximately 1 per 1000 between 1983 and 1987.[16] Neurosurgical practice in Japan, with widespread use of dura mater, may be different from other countries throughout the industrialised world and therefore it would seem unreasonable to extrapolate any estimated risk from these data. If neurosurgical practices in the UK were more akin to those in Australia, then a subsequent study by Brooke and co-workers would help provide additional information pertaining to estimated risk. By using information from the Australian CJD Surveillance system, Brooke and co-workers estimated the risk associated with exposure to human dura mater to be approximately 1 per 500 patients treated between 1978 and 2003.[17] Clearly, the risk of developing CJD in this patient population is considerably higher than we would expect by chance.

The human dura mater implicated in the transmission of CJD was processed, almost exclusively, by B Braun Melsungen in Germany and traded under the name Lyodura. Over 100 Japanese cases, and all but one of the UK cases (the source of the first case identified in the UK is unknown), have been associated with this particular product and only rarely has dura processed by other manufacturers been associated with transmission.[18 19] Although the first case in the UK was exposed to potentially infectious dura in 1969, a disproportionately large number of cases were exposed between 1983 and 1987 (80% of those identified worldwide and six of the seven cases in the UK). Interestingly, the apparent reduction in the number of cases post-1987 coincided with the introduction of stringent donor selection criteria and also the introduction of sodium hydroxide immersion techniques in the manufacturing process.

We found no temporal or geographical association between any of the dura-associated cases, or any other case of CJD identified in the UK, despite potential contamination of neurosurgical instruments.

It has been proposed that clinical features at onset are dependent on the site of graft placement or underlying parenchymal damage[20–22] and our findings may support such a proposition. The explanation for this observation is unclear. We, could, however, speculate that the pathological process starts within a region adjacent to the graft and that this is reflected in the early clinical features. This proposition may also be supported by findings obtained at autopsy, with severe pathological changes identified adjacent to graft placement in three cases. Overall, the pathology is consistent for that previously described in dura mater-associated CJD.[9 18] We did not identify either "kuru-type" or florid PrP plaques. The florid PrP plaques were previously noted in limited distribution in a small number of dural graft-associated iatrogenic CJD cases in Japan.[21 23 24]

We believe case VIII represents the first reported case of CJD in a person previously exposed to a graft from a non-human source. The age at onset, duration of illness, clinical and investigative features were similar to a typical case of sporadic CJD. Furthermore, the pathological features were also considered characteristic of sporadic CJD, with type 1 $PrP^{res}$ identified. Neither finding can definitively exclude the possibility of transmission of a yet unidentified pathogen. As natural transmissible spongiform encephalopathies are, however, as yet unrecognised in pigs, despite experimental transmission in animal models,[25] a chance association seems the most plausible explanation.

## ACKNOWLEDGEMENTS

We thank Jan MacKenzie for all her help in producing this manuscript. We also thank our colleagues within the European

surveillance programme for updated information, particularly Pascual Sanchez Jaun, and neurological colleagues throughout UK, particularly Dr Graham Lennox, for assistance with this manuscript. Finally, we thank our colleagues at the NCJDSU, particularly Alison Green, for carrying out CSF analysis, David Summers for advice on neuroimaging, and also Hester Ward and Katy Murray for comments on the manuscript.

**Authors' affiliations**
**C A Heath, M W Head, C Smith, J E Bell, J W Ironside, R G Will, R S G Knight,** National CJD Surveillance Unit, University of Edinburgh, Edinburgh, UK
**R A Barker,** Cambridge Centre for Brain Repair, University of Cambridge, Cambridge, UK
**T F G Esmonde,** Royal Victoria Hospital, Belfast, UK
**P Harvey,** Harley Street, London, UK
**R Roberts,** Ninewells Hospital, Dundee, UK
**P Trend,** The Royal Surrey County Hospital, Surrey, UK

Competing interests: None.

Correspondence to: Dr R S G Knight, National CJD Surveillance Unit, Bryan Matthews Building, Western General Hospital, Edinburgh EH4 2XU, UK; r.knight@ed.ac.uk

Received 7 June 2005
Revised version received 23 August 2005
Accepted for publication 24 August 2005

## REFERENCES

1 **Collins S,** Law MG, Fletcher A, *et al.* Surgical treatment and risk of sporadic Creutzfeldt-Jakob disease: a case-control study. *Lancet* 1999;353:693–7.
2 **Ward HJT,** Everington D, Croes EA, *et al.* Sporadic Creutzfeldt-Jakob disease and surgery: a case-control study using community controls. *Neurology* 2002;59:543–8.
3 **Will RG,** Ironside JW, Zeidler M, *et al.* A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996;347:921–5.
4 **Collinge J,** Sidle KCL, Meads J, *et al.* Molecular analysis of prion strain variation and the aetiology of 'new variant' CJD. *Nature* 1996;383:685–90.
5 **Bruce ME,** Will RG, Ironside JW, *et al.* Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. *Nature* 1997;389:498–501.
6 **Duffy P,** Wolf J, Collins G, *et al.* Possible person-to-person transmission of Creutzfeldt-Jakob disease. *New Engl J Med* 1974;290:692–3.
7 **Foncin JF,** Gaches J, Cathala F, *et al.* Transmission iatrogene interhumaine possible de maladie de Creutzfeldt-Jakob avec atteinte des grains de cervelet. *Rev Neurol* 1980;136:280.
8 **Prichard JW,** Thadani V, Kalb R, *et al.* Rapidly progressive dementia in a patient who received a cadaveric dura mater graft. *Morb Mortal Wkly Report* 1987;34:49–55.
9 **Thadani V,** Penar PL, Partington J, *et al.* Creutzfeldt-Jakob disease probably acquired from a cadaveric dura mater graft. *J Neurosurg* 1988;69:766–9.
10 **Will RG.** A new variant of Creutzfeldt-Jakob disease in the UK. *Proceedings of the Society for Veterinary Epidemiology and Preventative Medicine* 1997.
11 **Will RG,** Zeidler M, Stewart GE, *et al.* Diagnosis of new variant Creutzfeldt-Jakob disease. *Ann Neurol* 2000;47:575–82.
12 **Esmonde T,** Leuck CJS, Duchen LW, *et al.* CJD and lyophilised dura mater grafts: a report of two cases. JNNP 1991;56:999–1000.
13 **Willison HJ,** Gale AN, McLaughlin JE. Creutzfeldt-Jakob disease following cadaveric dura mater graft. *JNNP* 1991;54:940.
14 **Collie DA,** Sellar RJ, Zeidler M, *et al.* MRI of Creutzfeldt-Jakob disease: imaging features and recommended MRI protocol. *Clin Radiol* 2001;56:726–39.
15 **Tateishi J.** CJD transmitted through cadaveric dura grafts. *J Clin Exp Med* 1997:992–3.
16 **Nakamura Y,** Watanabe M, Nagoshi K. CJD associated with cadaveric dura mater grafts-Japan 1979–2003. *Morb Mortal Wkly Report* 2005;52:1179–81.
17 **Brooke FJ,** Boyd A, Klug GM, *et al.* Lyodura use and the risk of iatrogenic Creutzfeldt-Jakob disease in Australia. *Med J Aus* 2004;180:1–5.
18 **Pocchiari M,** Masullo C, Salvatore M, *et al.* Creutfeldt-Jakob disease after non-commercial dura mater graft. *Lancet* 1992;340:614–5.
19 **Hannah EL,** Belay ED, Gambetti P, *et al.* Creutzfeldt-Jakob disease after receipt of a previously unimplicated brand of dura mater graft. *Neurology* 2001;56:1080–3.
20 **Sato T.** CJD with dura mater transplantation. *Clin Neurol* 2003;43:870–2.
21 **Fushimi M,** Sato K, Shimizu T, *et al.* PLEDS in Creutzfeldt Jakob disease following a cadaveric dura graft. *Clin Neurophysiol* 2002;113:1030–5.
22 **Nishida y, Yamane M, Hara k, et al.** Creutzfeldt-Jakob disease after Jannetta's operation with cadaveric dura mater. *J Neurol* 2002;249:480–3.
23 **Takashima S,** Tateishi J, Taguchi Y, *et al.* Creutzfeldt-Jakob disease with florid plaques after cadaveric dural graft in a Japanese woman. *Lancet* 1997;350:865–6.
24 **Kimura K,** Nonaka A, Tashiro H, *et al.* Atypical form of dural graft associated Creutzfeldt-Jakob disease: report of a postmortem case with review of the literature. *JNNP* 2001;70:696–9.
25 **Castilla J,** Gutierrez-Adan A, Brun A, *et al.* Subclinical BSE infection in transgenic mice expressing porcine prion protein. *J Neurosci* 2004;24:5063–9.

別紙様式第 2-1
番号 14

医薬品
医薬部外品　　研究報告　調査報告書
化粧品

| 識別番号・報告回数 | | | 報告日 | 第一報入手日<br>2006 年 6 月 26 日 | 新医薬品等の区分<br>該当なし | 厚生労働省処理欄 |
|---|---|---|---|---|---|---|
| 一般的名称 | ①②ポリエチレングリコール処理人免疫グロブリン<br>③人免疫グロブリン | | 研究報告の公表状況 | The Lancet<br>2006; 367(9528):2068-2074 | 公表国<br>パプアニューギニア | |
| 販売名<br>(企業名) | ①献血ヴェノグロブリン-IH ヨシトミ（ベネシス）<br>②ヴェノグロブリン-IH（ベネシス）<br>③グロブリン-Wf（ベネシス） | | | | | |

**研究報告の概要**

＜背景＞
クールー病は、ヒトの流行性プリオン病について重要な経験を提供している。その発生は、1950 年代にパプアニューギニアでの感染ルート（部族内食人）の突然の中断の後、着実に減っていった。vCJD が発生し、英国において食事により広範囲に BSE プリオンへの曝露された後の感染率は不明であるために、クールー病が再び関心を呼ぶことになった。我々は、パプアニューギニアのクールー病患者における、潜伏期間、病因及び感染しやすさについての遺伝的要因について調査した。
＜方法＞
我々は、全ての疑わしい患者を調査するために、調査チームの規模を広げるとともに 1996 年にクールー病の監視を強化した。住民の居住歴と葬儀の宴での曝露歴の情報が、一連の神経学的検査とともに、可能な限り集められた。
＜結果＞
我々は、1996 年 7 月から 2004 年 6 月までに 11 人のクールー病患者を確認したが、全員が South Fore に住んでいた。患者は全員、1950 年代後半に食人習慣が中止される前に生れていた。最短の推定潜伏期間は、34 年から 41 年の範囲であった。しかし、男性における潜伏期間は 39 年から 56 年の範囲と考えられたが、実際はこれより最長で 7 年長かった可能性がある。プリオン蛋白の分析によって、殆どのクールー病の患者は、潜伏期間の延長とプリオン病への抵抗性に関連づけられている多形コドン 129 がヘテロ接合体の遺伝子型であった。
＜解釈＞
ヒトのプリオンに感染した場合の潜伏期間は、50 年を超える可能性がある。BSE プリオンにヒトが感染した場合、種を超えた場合の感染の特徴である「種の壁の効果」が、同じ種の中でのプリオンの感染と比較して、潜伏期間の平均値と範囲をさらに大きくするであろう。これらのデータは、vCJD の疫学モデルの作成の試みに影響を与えるはずである。

**使用上の注意記載状況・その他参考事項等**

代表として献血ヴェノグロブリン-IH ヨシトミの記載を示す。
2. 重要な基本的注意
(1)略
1)略
2)現在までに本剤の投与により変異型クロイツフェルト・ヤコブ病（vCJD）等が伝播したとの報告はない。しかしながら、製造工程において異常プリオンを低減し得るとの報告があるものの、理論的な vCJD 等の伝播のリスクを完全には排除できないので、投与の際には患者への説明を十分行い、治療上の必要性を十分検討の上投与すること。

| 報告企業の意見 | 今後の対応 |
|---|---|
| パプアニューギニアのクールー病患者の研究から、ヒトのプリオンに感染した場合の潜伏期間は、50年を超える可能性があることを示唆した報告である。<br>これまで血漿分画製剤によってvCJDを含むプリオン病が伝播したとの報告はない。しかしながら、万一vCJD感染者の血漿が本剤の原料に混入した場合には、製造工程においてプリオンを低減し得るとの報告があるものの、製剤から伝播する可能性を完全には否定し得ない。そのため、弊社の血漿分画製剤の製造工程におけるTSE感染性低減に関する検証実験を加速し、自社データを早期に取得し、工程評価を行い、必要に応じて工程改善を実施する予定である。 | vCJD の疫学情報については、今後も注視することとする。 |

# Kuru in the 21st century—an acquired human prion disease with very long incubation periods

John Collinge, Jerome Whitfield, Edward McKintosh, John Beck, Simon Mead, Dafydd J Thomas, Michael P Alpers

Lancet 2006; 367: 2068–74

MRC Prion Unit and Department of Neurodegenerative Disease, Institute of Neurology, University College London, London WC1N 3BG, UK (Prof J Collinge FRS, J Whitfield MSc, E McKintosh MRCS, J Beck BSc, S Mead MRCP, D J Thomas FRCP, M P Alpers FTWAS); Papua New Guinea Institute of Medical Research, Goroka, EHP, Papua New Guinea (J Whitfield); and Centre for International Health, Curtin University, Perth, Australia (M P Alpers)

Correspondence to: Prof John Collinge
j.collinge@prion.ucl.ac.uk

## Summary

**Background** Kuru provides the principal experience of epidemic human prion disease. Its incidence has steadily fallen after the abrupt cessation of its route of transmission (endocannibalism) in Papua New Guinea in the 1950s. The onset of variant Creutzfeldt-Jakob disease (vCJD), and the unknown prevalence of infection after the extensive dietary exposure to bovine spongiform encephalopathy (BSE) prions in the UK, has led to renewed interest in kuru. We investigated possible incubation periods, pathogenesis, and genetic susceptibility factors in kuru patients in Papua New Guinea.

**Methods** We strengthened active kuru surveillance in 1996 with an expanded field team to investigate all suspected patients. Detailed histories of residence and exposure to mortuary feasts were obtained together with serial neurological examination, if possible.

**Findings** We identified 11 patients with kuru from July, 1996, to June, 2004, all living in the South Fore. All patients were born before the cessation of cannibalism in the late 1950s. The minimum estimated incubation periods ranged from 34 to 41 years. However, likely incubation periods in men ranged from 39 to 56 years and could have been up to 7 years longer. *PRNP* analysis showed that most patients with kuru were heterozygous at polymorphic codon 129, a genotype associated with extended incubation periods and resistance to prion disease.

**Interpretation** Incubation periods of infection with human prions can exceed 50 years. In human infection with BSE prions, species-barrier effects, which are characteristic of cross-species transmission, would be expected to further increase the mean and range of incubation periods, compared with recycling of prions within species. These data should inform attempts to model variant CJD epidemiology.

Kuru is one of a group of closely related neurodegenerative conditions that affect both human beings and animals, known as the transmissible spongiform encephalopathies or prion diseases.[1] Prion diseases are associated with the accumulation in the brain of an abnormal, partly protease-resistant, isoform of a host-encoded glycoprotein known as prion protein (PrP). According to the protein-only hypothesis, an abnormal PrP isoform is the main, and possibly the only, constituent of the transmissible agent or prion.

The large-scale epidemic of bovine spongiform encephalopathy (BSE) in the UK led to fears of a serious threat to public health. Since 1996, cases of a novel human prion disease, variant Creutzfeldt-Jakob disease (vCJD), have been identified in the UK, and strain typing has confirmed that both vCJD and BSE are caused by the same prion strain.[1] Dietary exposure of the UK population to BSE prions has been widespread; the total cattle epidemic is thought to have affected 2 million cows.[2] Cattle BSE has also been reported in most EU states, Israel, Switzerland, Canada, the USA, and Japan. So far, about 160 vCJD patients have been identified in the UK, with cases also reported in France, Italy, Ireland, the Netherlands, Canada, Japan, and the USA. Predictions of the eventual size of a vCJD epidemic have varied widely, although some recent estimates, based on current cases of vCJD, suggest that the total epidemic may be relatively small.[3] However, key uncertainties, notably with respect to major genetic effects on the incubation period,[4] suggest the need for caution. Importantly, such models cannot estimate the number of infected individuals, which remains unknown, and concerns of secondary transmission have heightened.[5] These uncertainties, especially with the possibility of very long incubation periods of BSE in people, have renewed interest in kuru, which remains the only example of a major human epidemic.

Kuru reached epidemic proportions in a defined population of the Eastern Highlands of Papua New Guinea. Local oral history, taken when the disease was first studied by western medicine in the 1950s, dated the onset of the first cases to the 1920s. Kuru mainly affected the people of the Fore linguistic group and also their neighbours with whom they intermarried. The disease predominantly affected women and children (of both sexes), with only 2% of cases in adult men;[6] kuru also became the most common cause of death in women in affected villages. Kuru is a cerebellar syndrome with a characteristic and relentless progression through defined clinical stages, and is invariably fatal. Cognition is fairly preserved, and the disease is highly distinctive and is usually recognised easily by both the patients and their local community.[6]

These communities practised the consumption ritual of dead relatives as a mark of respect and mourning. Boys older than 6–8 years participated little in mortuary